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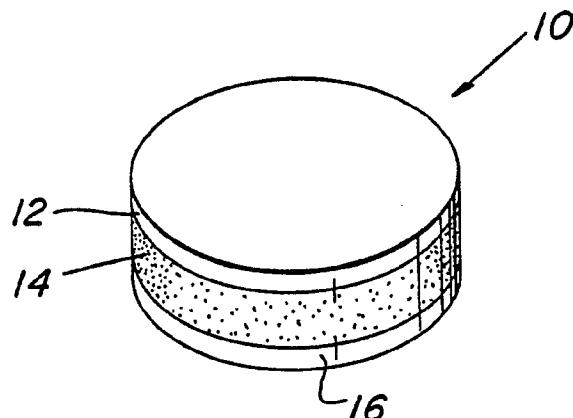
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(54) Estradiol transdermal delivery system.

(57) The present invention is directed to a transdermal delivery system (10) for an active substance. The active substance is estrogen or its derivatives and preferably is 17-beta-estradiol. The system (10) comprises an impermeable backing layer (12) and a matrix (14) affixed thereto. The matrix (14) comprises, on a weight percentage basis, from about 60 to about 95% of an adhesive polymer, from about 5 to about 20% of a solvent, from about 0.2 to about 4% of a skin penetration enhancer, and from about 0.5 to about 5% of the active substance. The system is free of any discrete permeable, polymeric, diffusion-controlling membrane.

FIG. 1



ESTRADIOL TRANSDERMAL DELIVERY SYSTEM

Scope of the Invention

The present invention is directed to a transdermal (or percutaneous) delivery system for estrogen and its derivatives. This delivery system is a drug-containing adhesive device which has a constant release rate over a period of time.

Background of the Invention

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Estradiol is the predominant estrogen secreted by the ovary during the reproductive era. The initial decline in ovarian function during perimenopause ultimately leads to an almost complete cessation of ovarian production of estrogens in the postmenopausal years. Thus, postmenopausal women are deficient principally in estradiol.

It is well recognized that in some women this deficiency rapidly results in the development of vasomotor symptoms and in atrophic changes within the genital tract. Additionally, certain psychological symptoms - such as anxiety, forgetfulness and difficulty in concentrating (i.e. "menopausal syndrome") - increase in frequency during the climacteric and early postmenopausal years. Ovarian failure also has long-term consequences because postmenopausal women are at an increased risk of developing osteoporosis and certain fractures.

Replacement of estrogen during the climacteric and postmenopausal period not only relieves all the acute symptoms but also appears to protect against both the development of osteoporosis and the occurrence of the fractures.

Currently, exogenous estrogen therapy is mainly prescribed by the oral route of administration: this therapy has certain disadvantages. High doses of estrogen must be administered because of the rapid metabolism and inactivation of estrogens by the gut wall and liver (first pass effect). It has been estimated that up to 30% of the administered dose is inactivated even before it reaches the systemic circulation.

The potential advantage of delivering estradiol transdermally is that gut wall and hepatic metabolism may be avoided, thus not only allowing the use of lower total daily doses but also diminishing the risks of hepatic enzyme induction and its sequelae. Transdermal delivery of estradiol can control menopausal symptoms effectively without inducting adverse metabolic changes.

U.S. Patent No. 4,379,454 discloses a transdermal delivery system for estradiol. This system is a permeable membrane-controlled reservoir system that uses ethanol as a skin penetration enhancer. The estradiol is dissolved in the ethanol and both penetrate through the skin. A permeable membrane is used for containing the diffusion rate. An adhesive is applied on the permeable membrane. The stability of this system is short and the delivery rate is not constant. Moreover, the enhancer, ethanol, reacts with adhesive and causes loss of adhesion and, consequently, the system falls off the skin.

U.S. Patent No. 4,390,520 discloses a transdermal delivery system for indomethacin. This system is a drug-containing adhesive device. The system comprises, in relevant part, indomethacin and a skin penetration enhancer, polyoxyethylene sorbitan mono-oleate ("polysorbate"), which are mixed into a adhesive copolymer, such as 2-ethylhexyl acrylate-vinyl acetate copolymer. The indomethacin is dissolved directly into the copolymer.

U.S. Patent No. 4,420,470 discloses a transdermal delivery system for drugs useful in suppressing or preventing attacks of angina pectoris; the drugs are isosorbide dinitrate and pentaerythritol tetranitrate. This system is a drug-containing adhesive device. The system comprises, in relevant part, the drug and skin penetration enhancer, such as polyethylene glycol, mixed with an adhesive copolymer, such as 2-ethylhexyl acrylate-vinyl acetate copolymer.

U.S. Patent Nos. 4,291,014; 4,321,252; and 4,438,139, which are deemed cumulative of one another, each disclose a transdermal delivery system for estrogen-type drugs. These systems are generally monolithic-type devices, i.e., an adhesive is interposed between the skin and matrix. For example, U.S. Patent No. 4,438,139 discloses a matrix comprising a polar plasticizer, polyvinyl alcohol, polyvinyl pyrrolidone and estrogen. The polar plasticizer is polyethylene glycol and is necessary to make the matrix flexible and to increase the reliability of diffusional release of the estrogen. Additionally, a detergent (i.e. surfactant), such as sorbitan, and an absorption facilitator, may be added.

- U.S. Patent Nos. 4,058,122 and 4,077,407, which are deemed cumulative of one another, each disclose a drug delivery system for estrogen. These systems are generally reservoir-type devices. For example, U.S. Patent No. 4,058,122 discloses a system comprising a wall, having a passageway, which surrounds an active agent. In operation, the wall is permeable to external fluids which cross through the wall and which
- 5 create an osmotic pressure within the wall. The osmotic pressure forces the drug from behind the wall and through the passageway. Materials which are added to the wall (lamina) to control flux through the wall include polyethylene glycol. Dispersants, which are added to the wall to produce an integral composite, include polyoxyethylenated sorbitan oleate having 5 to 20 moles of ethylene oxide.

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Summary of the Invention

The present invention is directed to a transdermal delivery system for an active substance. The active substance is estrogen or its derivatives and preferably is 17-beta-estradiol. The system comprises an impermeable backing layer and a matrix affixed thereto. The matrix comprises, on a weight percentage basis, from about 60 to about 95% of an adhesive polymer, from about 5 to about 20% of a solvent, from about 0.2 to about 4% of a skin penetration enhancer, and from about 0.5 to about 5% of the active substance. The system is free of any discrete permeable, polymeric, diffusion-controlling membrane.

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Description of the Drawings

25 For the purpose of illustrating the invention, the drawings show a form in which is presently preferred; it being understood, however, that this invention is not limited to the precise arrangements and instrumentalities shown.

- Figure 1 is an isometric view of a preferred embodiment of the present invention.
 Figure 2 is a sectional view taken generally along lines 2-2 in Figure 1.
 30 Figure 3 is a graph illustrating the results of a hairless mouse skin flux study.
 Figure 4 is a graph illustrating the results of a human cadaver skin flux study.

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Detailed Description of the Invention

In the present invention, the transdermal delivery system 10 comprises an impermeable backing membrane 12, a polymeric diffusion matrix 14 which is preferably formed by one or more thin layers 40 (illustrated in phantom) and is free of any discrete polymeric diffusion membrane. An example of such a diffusion membrane is set forth in U.S. Patent No. 4,379,454 incorporated herein by reference. The impermeable backing membrane is well known in the art and is not limiting on the instant invention.

The matrix 14 is compounded on a weight percentage basis, from about 60 to about 95% of an adhesive polymer, from about 5 to about 20% of pharmaceutical grade solvent, from about 0.2 to about 4% 45 of a skin penetration enhancer and from about 0.5 to about 5% of an active substance.

The adhesive polymer is a pressure sensitive adhesive and is acceptable for medical use. Of these types of polymer, either water base or solvent base materials may be used. These polymers have two functions in the instant invention. First, they are adhesive to the skin and securely hold the matrix on and in good diffusional contact with the skin. Second, they are the carrier or vehicle for storing the active 50 substance. Preferably, the adhesive polymer is a vinyl acetate - acrylate multipolymer. Such a multipolymer is commercially available from the Monsanto Company, St. Louis, MO, under the name of GELVA®. GELVA® 737, 788 and 2484 may be used. Specifically, GELVA® 737 comprises up to 1.1% of 2-ethylhexyl acrylate and the balance vinyl acetate.

The active substance which is transdermally delivered to the systematic circulation of the body in 55 therapeutically effective amounts is preferably 17-beta-estradiol. However, any estrogen or estrogen derivative, which are well known, may be used.

The solvent dissolves the active substance. The solvent is polyethylene glycol or polyethylene glycol esters or propylene glycol or combinations thereof. Polyethylene glycol, as used herein, means polyethyl-

ene glycol with average molecular weights of 200, 300, 400, 500 600 and 800 and its derivatives. Polyethylene glycol esters, as used herein, means polyethylene glycol monolaurate, polyethylene glycol mono-oletate and polyethylene glycol monopalmitate. The solvents described herein are commercially available from such companies as Emery Industries and BASF.

5 The skin penetration enhancer is a polyoxyethylene ethers, preferably polysorbate 80, i.e. sorbitan mono-9-octadecenoate poly (oxy-1,2-ethanediyl) and its derivatives. However, other polysorbates, such as polysorbate 21, 40, 60, 61, 65, 80, 81 and 85, may be used. Additionally, polyoxyethylene ethers of higher aliphatic alcohols, such as BRIJ® 52, 56, 58, 30, 35, 92, 96, 98, 72, 76, 78, 700, 721 and etc., may be used. BRIJ® is a trademark of ICI United States, Inc. of Delaware. Polysorbate 80 is a product of ICI, Wilmington, 10 Delaware.

In operation, the system is applied to the skin where the adhesive polymer affixes the system on the skin. The active substance, which is dissolved by the solvent, is disbursed throughout the matrix. The active substance diffuses from the matrix with the enhancer. At the stratum cornium, the enhancer facilitates the transdermal diffusion therethrough and into the systemic circulation. the transdermal flux of the active 15 substance is substantially uniform. See Figures 3 and 4.

The preparation of the transdermal delivery system according to the present invention is accomplished as follows. The active substance is dissolved in the solvent and enhancer to form a solution. The solution is added to the polymer and mixed for about 20-30 minutes and then allowed to stand for about 20-60 minutes to eliminate the air bubbles. This mixture is cast on the impermeable membrane, a polyethylene 20 film or aluminized polyethylene film made by 3M Company (e.g. 3M-Scotchpak 1006 or 3M-1012) and dried at about 40 °C to 50 °C, for about 20-40 minutes. After drying the coating, a release liner 16, such as a silicon release paper or the like which are well known, is placed over the exposed surface of the matrix. Then the system is die cut into a optimum size. If multiple matrix layers are required, each subsequent 25 layer is cast over or overlaps the previous layer. The finished system is put into a pouch and hermetically sealed.

Example 1

30 To prepare the matrix, 0.2 g of 17 beta-estradiol is dissolved in 0.5 g of polyethylene glycol 200, 0.25 g of propylene glycol and 0.05 g of polysorbate 80, whereby a solution is formed. This solution is added to 10 g of polymer solution (Monsanto GELVA® 737) and then mixed for 20-30 minutes. After mixing, the mixture is settled for about 20 minutes to remove air bubbles and is cast onto the backing material (3M-Scotch Pak 35 1006 or 1012). The cast mixture is dried from 30 minutes at 45 °C. To make a triple layers matrix, the 2nd and 3rd layers are sequentially cast over the prior layer after the prior layer is settled and dried. This formation is then cut into 4cm² shapes.

Hairless mouse skin flux study results for this matrix formulation are shown on Table 1.

40 Example 2

0.1 g of 17 beta-estradiol is dissolved in 1.0 g of polyethylene glycol 400 and 0.01 g of polysorbate 60. 45 This solution is mixed with 12 g of polymer solution (Monsanto GELVA® 788) for 25 minutes. After settling for 20 minutes, the mixture is cast onto the backing material. The remaining steps are the same as set forth in Example 1.

50 Example 3

0.4 g of 17 beta-estradiol is dissolved in 6 g of polyethylene glycol 400, 2 g of propylene glycol and 0.5 g of diethylene glycol oleyl ether. This solution is mixed with 30 g of polymer solution (Monsanto GELVA® 55 2484) for 20 minutes. The remaining steps are set forth in Example 1.

Example 4

5 0.5 g of 17 beta-estradiol is dissolved in 4 g of polyethylene glycol 400, 3 g of propylene glycol and 0.5 g of polysorbate 20. This solution is mixed with 20 g of polymer solution for 30 minutes. After settling for 20 minutes, the further steps set forth in Example 1 are followed.

The human cadaver skin flux study, results for this formulation are set forth in Table 2.

Example 5

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0.7 g of 17 beta-estradiol is dissolved in 15 g of polyethylene glycol 400, 0.5 g of polysorbate 60 and 3 g of propylene glycol. This solution is mixed with 25 g of polymer solution (Monsanto GELVA® 737) for 25 minutes. The remaining steps are the same as set forth in Example 1.

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Example 6

20 0.3 g of 17 beta-estradiol is dissolved in 6 g of polyethylene glycol 400 monolaurate and 0.5 g of BRIJ® 92. This solution is mixed with 30 g of polymer solution for 30 minutes. After settling for 20 minutes, the remaining steps are the same as set forth in Example 1.

25 The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

Table 1

Hairless Mouse Skin Flux Study				
(ug - micrograms)				
Time (hr)	Sample No. 1	Sample No. 2	Average	
35 24	5.913 ug	4.323 ug	5.118 ug	
	15.565 ug	9.563 ug	12.609 ug	
	14.207 ug	10.985 ug	12.596 ug	
	8.904 ug	7.358 ug	8.131 ug	

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Table 2

Human Cadaver Skin Flux Study				
(ug - micrograms)				
Time (hr)	Sample No. 1	Sample No. 2	Average	
50 24	5.276 ug	2.554 ug	3.915 ug	
	12.432 ug	7.737 ug	10.085 ug	
	13.006 ug	5.376 ug	9.191 ug	
	5.053 ug	6.206 ug	6.030 ug	

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Claims

1. A transdermal delivery system (10) characterized by:
a impermeable backing layer (12);
- 5 a matrix (14) affixed to said backing layer (12) and comprising on a weight percentage basis from about 60 to about 95% of an adhesive polymer, from about 5 to about 20% of a solvent, from about 0.2 to about 4% of a skin penetration enhancer, and from about 0.5 to about 5% of an active substance; and
said system being free of any discrete, permeable, polymeric, diffusion-controlling membrane.
- 10 2. The system according to claim 1 wherein said active substance is selected from the group consisting of estrogen, derivatives of estrogen and combinations thereof.
- 15 3. The system according to claim 1 wherein said active substance is 17-beta-estradiol.
4. The system according to claim 1 wherein said adhesive polymer is a vinyl acetate-acrylate multipolymer.
- 15 5. The system according to claim 1 wherein said solvent is selected from the group consisting of propylene glycol, propylene glycol derivatives and combinations thereof.
- 20 6. The system according to claim 1 wherein said solvent is selected from the group consisting of polyethylene glycol having approximate molecular weights of 200, 300, 400, 500, 600 and 800, and polyethylene glycol ester such as polyethylene glycol monolaurate, mono-oleate, and monolaurate, and combinations thereof.
- 25 7. The system according to claim 1 wherein said skin penetration enhancer is a polyoxyethylene ester.
8. The system according to claim 1 wherein said skin penetration enhancer is sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) and its derivatives.
9. The system according to claim 1 further characterized by a release layer (16), whereby said matrix (14) is sandwiched between said backing layer (12) and said release layer (16) prior to use.
- 25 10. A transdermal delivery system (10) characterized by:
an impermeable backing layer (12);
a matrix (14) affixed to said backing layer (12) and comprising on a weight percentage basis from about 60 to about 95% of an adhesive polymer such as vinyl acetate-acrylate multipolymer, from about 5 to about 20% of a solvent selected from the group consisting of propylene glycol, propylene glycol derivatives and combinations thereof, from about 0.2 to about 4% of a skin penetration enhancer such as a polyoxyethylene ester, and from about 0.5 to about 5% of an active substance selected from the group consisting of estrogen, derivatives of estrogen and combination thereof; and
said system being free of any discrete, permeable, polymeric, diffusion-controlling membrane.

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FIG. 1

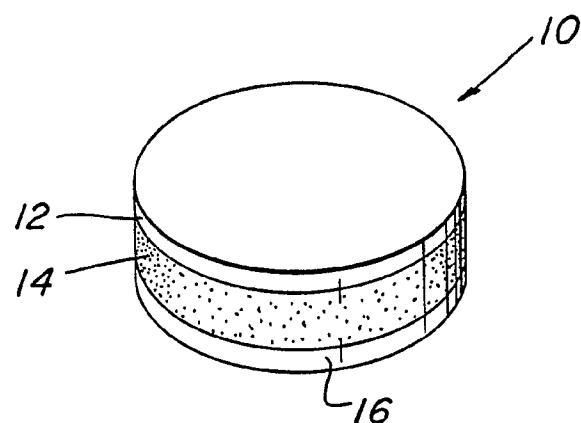
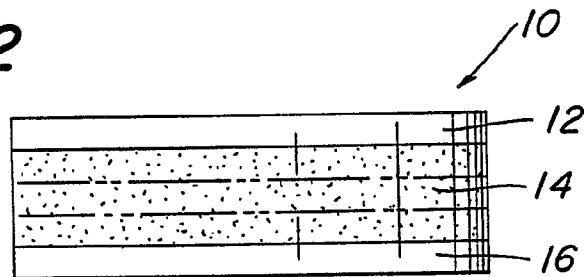


FIG. 2



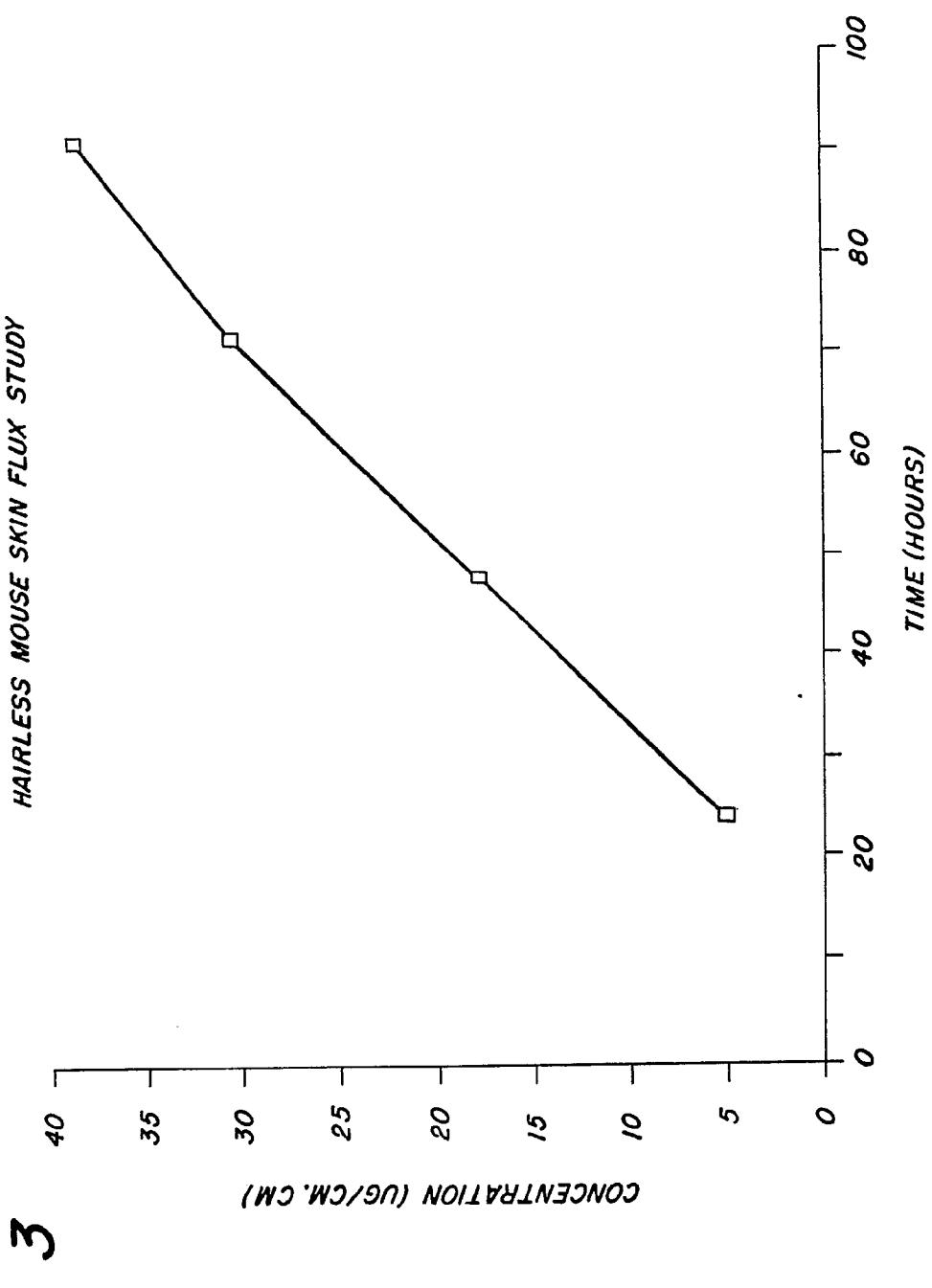
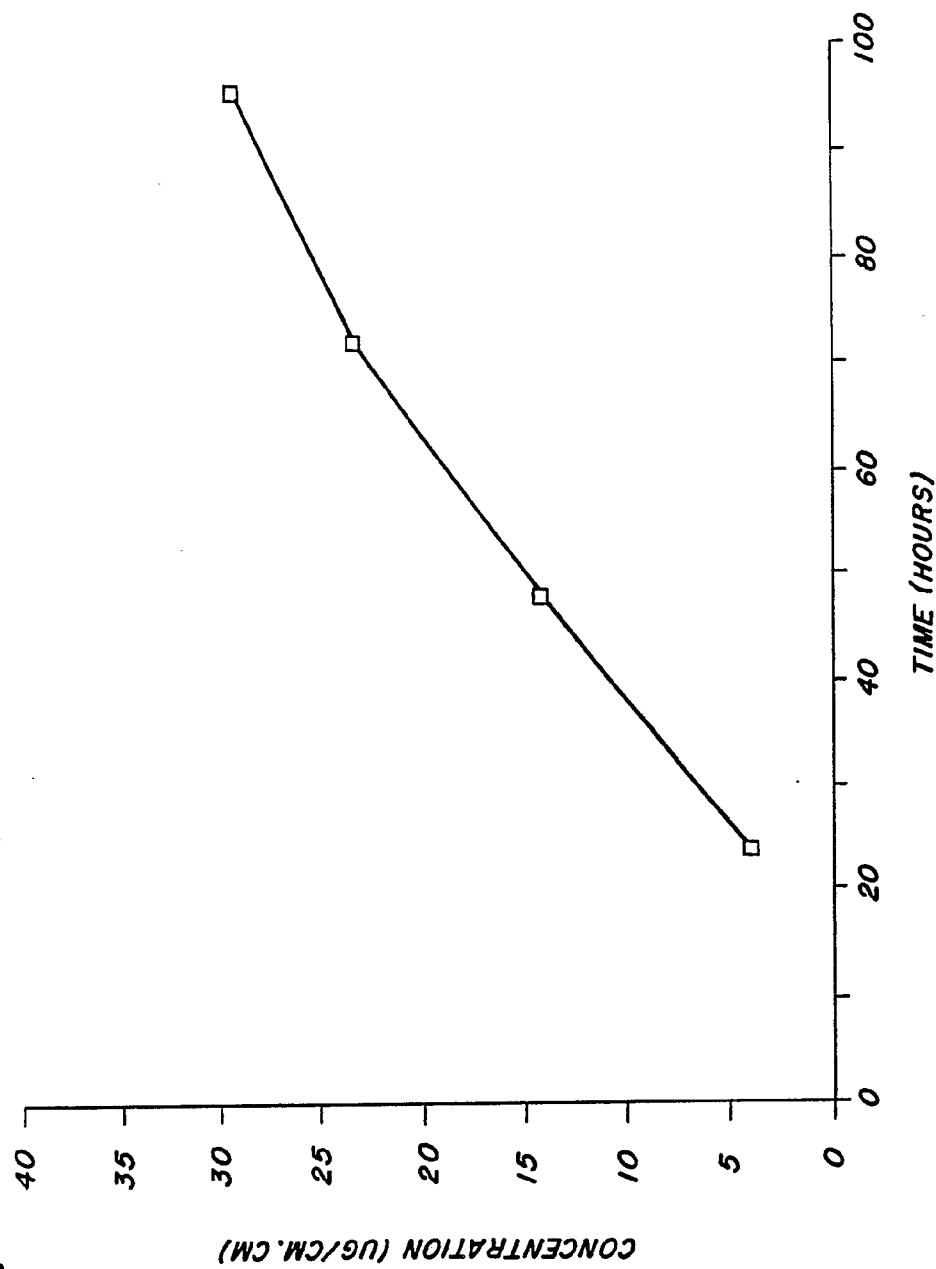


FIG. 4

HUMAN CADAVER SKIN FLUX STUDY





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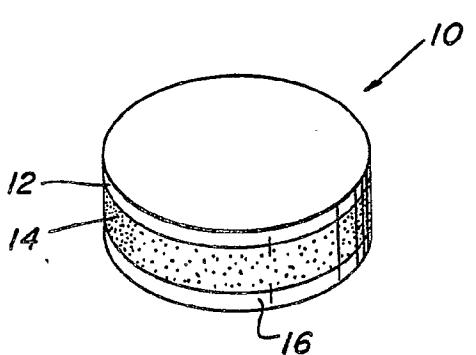
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㉛ Estradiol transdermal delivery system.

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FIG. 1



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EP 88 30 6394

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	EP-A-0 156 080 (NITTO ELECTRIC INDUSTRIAL CO., LTD) * Page 11, lines 16-19; page 15, line 2; page 18, lines 8-16; page 19, lines 13-17 *	1-10	A 61 K 9/70 A 61 L 15/03 A 61 M 37/00
D, Y	GB-A-2 086 224 (NITTO ELECTRIC INDUSTRIAL CO., LTD) * Page 2, lines 15-18; page 3, lines 3-31; example 3; claim 15 *	1, 4, 7-8 , 10	
Y	EP-A-0 223 524 (NITTO ELECTRIC INDUSTRIAL CO., LTD) * Page 3, lines 1-42; page 5, line 4; page 5, lines 55-58; claims 1-14 *	1-6, 9-10	
A	JOURNAL OF CONTROLLED RELEASE, vol. 2, no. 1/4, November 1985, pages 111-120, Elsevier Science Publishers B.V., Amsterdam, NL; A. HOELGAARD et al.: "Dermal drug delivery - improvement by choice of vehicle or drug derivative" * Abstract; page 112; table 2 *	1-2, 5-6	
A	N.T.I.S. TECH NOTES, December 1987, page 1216, Springfield, VA., US; "Research shows that transdermal (Skin) patch may be an improved method of administering hormones"		A 61 L
P, A	EP-A-0 272 987 (CYGNUS RESEARCH CORP.)		
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	02-11-1989	ESPINOSA Y CARRETERO M.	
CATEGORY OF CITED DOCUMENTS			
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